CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-358

CORRESPONDENCE

Pharmaceuticals, Inc. [illegible] Tampa FL 33637 813 975 7700 Fax 813 975 7770

January 21, 2000

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Minor Amendment

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's December 10, 1999 "Not Approvable" letter for the above referenced application. In that letter the Agency indicated that our response would be considered a minor amendment. A copy of the letter is provided in Attachment 1.

To facilitate the Agency's review, the Agency's comments and our corresponding response are provided in the text of this letter. Necessary supporting documentation for our response is provided in attachments to this amendment.

Agency Comment: Based on the information provided in your amendment dated 11/04/99, we believe that the contamination of in your drug product is of concern. We believe that you have two options:

- **Provide a safety information package for based on the inhalation administration at the concentration level found in your product. We will send it to the Division of Pulmonary Drug Products for consultation.**

- **Or you may obtain a new overwrap/pouch system supported by adequate analytical data to demonstrate that it will not contaminate the drug product solution with any volatile chemicals. Chromatographic profiles are requested comparing freshly manufactured solution versus solution stored in the exact market configuration for at least 3 months at 40°C. The sensitivity of the methods should be demonstrated to be approximately 100 ppb using marker compounds. Alternatively, you may provide documentation that the pouch you propose to use has been approved by the FDA for marketing an inhalation solution in . We may consider alternate scientific approaches to address this issue.**

Response: We have obtained data which demonstrates that is present in a currently marketed inhalation product at concentrations equal to or greater than those in our product. Specifically, we have tested samples of the currently marketed inhalation product n (cromolyn sodium inhalation solution) and determined that the maximum concentration in the Bausch & Lomb product is slightly less than the maximum observed in unstressed Solution obtained from the marketplace.

α- Solution	
Sample Description	**Concentration**
Maximum value observed for Bausch & Lomb Pharmaceuticals' Albuterol Sulfate Inhalation Solutions stored in pouched for 23 Months under accelerated (25 ± 2°C) conditions	

Not quite what I said HB 2/3/00

As indicated by Mike Smela during the December 15, 1999 teleconference between Bausch & Lomb and the Agency, this fact alone is sufficient to warrant demanding immediate approval or our application.

Copies of the spectra for the samples are provided in Attachment 2. Copies of the spectra previously provided for Bausch & Lomb Albuterol Sulfate Inhalation Solution are also included. The methods used for detection and quantitation of for cromolyn sodium inhalation solution and for albuterol sulfate inhalation solution) are essentially the same. Copies of the methods and the validations for both procedures are provided in Attachment 3.

The equivalence of the packaging materials is further demonstrated by the following table which compares pouch material from currently marketed Solution (cromolyn sodium inhalation solution,) and the proposed pouch material for Bausch & Lomb Pharmaceutical's Albuterol Sulfate, USP Inhalation Solution, 0.083%. As indicated by the table, they differ only in the manufacturer of the liner material and minor variations in the thickness of the layers.

November 6, 1998

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Major Amendment

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's September 29,1998 "not approvable" letter for the above referenced application. In that letter the Agency indicated that our response would be considered a major amendment.

To facilitate the Agency's review, each of the questions and our corresponding response is provided in the text of this letter. Necessary supporting documentation for each response is provided in attachments to this amendment.

A1. Please update your acceptance criteria for Sodium Chloride USP and Purified Water USP per current USP 23.

Response: The specifications for Sodium Chloride USP and Purified Water USP were revised to comply with current USP (supplement 8) after the supplement was issued in May of this year. Copies of the revised specifications are provided in Attachment 1.

A2. Please include a proper in-process specification for in the compounding stage (p.759). It needs to have three digits after the decimal, to be consistent with the target value of .. Please also include the temperature condition for the Density testing.

Response: The in-process specification for has been revised as requested. A copy of the revised In-Process Test Summary is provided in Attachment 2. The temperature conditions for density testing (25 ± 0.5°C) are specified in method on page 1204 of the original application (The current revision is provided in Attachment 2).

A3. Please notice that the unit for "Specific Gravity" is incorrect on page 744.

Response: As noted by the reviewer the units were incorrectly stated as g/mL. This was also noted by Bausch & Lomb personnel during the manufacture of the exhibit batch and the error was corrected in the Master Batch Record provided in the original application (see pages 215 & 217, provided in Attachment 3).

A4. Please explain why you used Density for the calculation during the compounding stage and then used Specific Gravity at the filling stage.

Response: As noted by the reviewer, product density was measured at the in-process testing stage but specific gravity was used to calculate the weights corresponding to the fill volume target and limits (page 788 of the original application).

The instrument used to measure density also provides the specific gravity. This value is recorded on the In-Process Test Summary Sheet by the analyst at the same time as the density. The Fill Volume Record form in use at the time incorrectly specified the use of specific gravity.

We believe that density is the appropriate parameter for calculation of the fill values and the Fill Volume Record form (provided in Attachment 4) has been revised to use the measured density.

A5. Please state your intention if the pH is below the target during the compounding stage.

Response: As noted by the reviewer, the product formulation does not permit addition of any reagent to raise pH. If the product pH measured during compounding is below the target range specified in the Compounding Instructions a Material Evaluation Report (MER) would be initiated and an investigation would be performed in accordance with procedure (provided in Attachment 5). If the pH is within the In-Process Release Specification range and the investigation reveals no other reason to abort the compounding process, the manufacturing process may continue. If the pH is outside the In-Process Release Specification range or the investigation reveals any other issue which makes the integrity of the batch questionable, the manufacturing process will be discontinued and the batch will be discarded.

A6. The total accountabilities for the finished packages are not very clear. Please provide accountabilities of all package configurations (before and after repouching for the executed batch).

Response: As noted by the reviewer, the batch record used for the exhibit batch did not provide a clear method for accountability of pouched units. In addition, all

units were repackaged due to a seal defect noted in some pouches. Because the product was repackaged immediately after the initial pouching operation and because all units were repackaged, no accountability was performed between the initial pouching and the repackaging. However, because all units were repackaged, the accountability performed after the repouching also reflects all the units initially packaged (i.e., the number of units initially packaged is the same as the number of units reported in the accountability performed after repouching).

The following table identifies the number of units which were packaged in each configuration:

Configuration	4 Units per Pouch	28 Units per Pouch	60 Units per Pouch
Number of Pouches			
Number of Units			

These totals were calculated from the information on page 843 of the application. To further clarify the accountability of packaged product, the number of packaged units is compared in the following table to the number of units delivered from filling. The number of units delivered from filling was determined from the Filled Product Accountability Record on page 792 of the original application (provided in Attachment 6).

Step	Description	Product Number (Package Configuration)			Total
		37405/05ZX (4 units/pack)	37460/05ZX (28 units/pack)	37474/05ZX (60 units/pack)	
A	Number of units delivered to Packaging				
B	Number of units rejected during packaging.				
C	Number of units taken as packaged samples				
D	Number of packaged units delivered				
E	Total Number of Units Packaged (C+D)				
F	Variance [(E/A) – 1] X 100				

To provide positive accountability of packaged product in future batches, a packaged product accountability form (FFSPAR374) has been added to the batch

record. A copy of the form is provided in Attachment 6. The Filled Product Accountability Form has also been revised to better correspond to the way the product accountability is actually performed for form/fill/seal products. The product is filled into cards consisting of 6 groups of 4 vials each. After filling, the waste plastic (flashing) between the groups of vials is removed to separate the 4 vial packets (referred to as 4 ups). The 4 ups are handled as single entities during packaging so that the finished product consists of packages containing multiples of the 4 unit packets.

A7. Please explain the large loss (about of the batch) for " d" in the filling stage.

Response: During the manufacture of the exhibit batch we experienced difficulty maintaining the alignment of the used to remove excess plastic from the cards containing the filled vials. As a result, a number of the vials exhibited minor cosmetic defects which caused them to be rejected. It should be noted that this product is packaged in groups of 4 connected vials (referred to as 4 ups). A cosmetic defect in one vial will result in the entire 4 up being rejected, even if the remaining vials are acceptable.

A8. Please include a specification for "" " of the vials into your In-Process Control in the filling stage.

Response: The filling instructions (provided in Attachment 8) have been revised to include a specification of for "" ," of the vials. Refer to step 19 on page 4 of the revised instructions.

A9. Please revise your acceptance specification for the ' esin to include the Physicochemical Tests for Plastics under USP <661>.

Response: As noted by the reviewer, USP <661> describes physicochemical testing to be performed for plastic containers. We concur that this testing should be performed and have provided the results in the original application (page 941). It should be noted, however, that the European Pharmacopoeia is specific to materials for the manufacture of containers and requires more stringent testing of the resin. The European Pharmacopoeia also includes tests which are similar to each of the tests specified in USP <661>. The table which follows lists the USP <661> tests and identifies the EP test which performs a similar function.

USP <661> Containers (Physicochemical Tests- Plastics)	EP General Methods - 3.1 Materials Used for the Manufacture of Containers (3.1.4 Polyethylene without Additives for Containers for Parenteral and Ophthalmic Preparations)
Buffering Capacity	Acidity/Alkalinity
Non-volatile residue	Substances soluble in hexane
Residue on ignition	Sulphated ash
Heavy Metals	Extractable Heavy Metals

Our present acceptance specification (provided in Attachment 9) includes these and additional EP requirements which provide a more complete evaluation of the resin than that specified by USP <661>. We propose to continue employing these more detailed specifications for the testing of each lot of the LDPE resin.

A copy of the Physicochemical Test Results from the original application and the applicable sections from the United States Pharmacopoeia 23, Chapter <661>, and the European Pharmacopoeia 3rd Edition, 1998 Supplement, are also provided in Attachment 9.

A10. Please acknowledge that prior approval supplement is needed to add a new manufacturer for the resin.

Response: Bausch & Lomb Pharmaceuticals acknowledges that a prior approval supplement is needed to add a new manufacturer for the esin.

A11. Please provide a complete COA for the Resin, with all specifications/test results, from the vendor.

Response: As requested by the reviewer, we have attempted to obtain from the vendor complete COA for the esin used to manufacture the exhibit batch. We have been informed by hat they perform only the "melt index" and "density" test for release of individual batches of resin. They have performed Physicochemical and Biocompatibility testing and the results are available in their DMF ut they do not perform these tests on a routine basis. A copy of the letter from s provided in Attachment 11.

A12. Please include additional testing into your finished product controls:

a) A second identification test for the Albuterol in the finished product as you have used a non-specific analytical method for identification.

b) **APHA testing for the color of the solution (or correlate APHA values to the proposed BP scale).**

c) **Fill Volume**

Response:

(a) As requested by the reviewer, the following additional identification test has been added to the Finished Product Specifications(provided in Attachment 12):

Test Description	Method	Acceptance Criteria
Identification		

It should also be noted that the identification test utilized for albuterol in the finished product is a method which is specific for the analyte of interest.

(b) A correlation study between BP and APHA color standards has been performed as requested by the reviewer. This study suggests the following correlation of BP Reference Standard ranges to the APHA specification ranges:

BP Color Reference Standard	Associated APHA Values
BY1	1200-1600
BY2	900-1000
BY3	460-700
BY4	200-280
BY5	120-160
BY6	40-80
BY7	10-50

Each BP Color Reference Standard represents a range of APHA values because there is some subjective variability associated with the evaluation of these values.

Since a correlation between the BP Color Reference Standard and APHA standards has been established, we plan to continue using the BP compendial method to determine color. The chosen method is a well accepted compendial method in the BP as well as the European Pharmacopoeia.

(c) As requested by the reviewer, a specification for fill volume has been added to the Finished Product Specifications. Copies of the revised specifications, the Final

Chemical Test Summary and the test procedure [redacted] are provided in Attachment 12.

It should also be noted that in-process controls, specified in the Filling Instructions in Attachment 8, ensure that fill volume control is achieved. This is specifically addressed in the manufacturing setting by use of the [redacted] hart for Fill Volume/Weight measurement. This control is exercised throughout the manufacturing process and the compliance to this specification is a quality control parameter.

A13. Item 12(b) is applicable for stability testing.

Response: A correlation between the BP and APHA color scales has been established, as requested by the reviewer. The correlation is described in our response to Chemistry Question A.12.b. Thus, for the purpose of stability testing Bausch & Lomb Pharmaceuticals plans to continue using the BP compendial method to determine color.

A14. Please include a resolution requirement in system suitability for your method, [redacted] Please also use a solution, which is made for limit of detection, in the system suitability to ensure reliability of the method for detection of impurities.

Response: As requested by the reviewer, method [redacted] ovided in Attachment 14) has been revised to include a resolution requirement. The resolution requirement, specified in section V.C.2 (page 5) of the method, is: " between albuterol and 1-(n-4;dihydroxy-3-hydroxymethyl-phenol)-2-(tert-butylamino) "

Method [redacted] section V.A.4.a (page 3), includes a system sensitivity solution prepared to be [redacted] of the label claim of albuterol. This solution is used to evaluate the [redacted] criteria for system suitability and ensure reliability of the method for detection of impurities.

A15. The stability data sheets are lacking the "Batch Size" and "Actual Date of Testing" for each time station. Please include this information.

Response: As requested by the reviewer, we have prepared stability data sheets which include the batch size and actual date of testing for each time station. Copies of the revised stability data sheets are provided in Attachment 15.

As requested by the Agency, Bausch & Lomb Pharmaceuticals also acknowledges:

BI. The Agency's request for additional stability data. Stability data available to date is provided in Attachment 15.

B2. That the cGMP status of the firms referenced in the ANDA will be evaluated by FDA's Office of Compliance and an adequate evaluation is required prior to approval.

B3. That our sterility assurance information is pending review.

B4. That our response must also address the labeling deficiencies. Labeling issues are addressed in Attachment 16.

B5. That a satisfactory methods validation is required to support the ANDA and that the study will be scheduled once the testing issues are resolved.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's September 29,1998 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-358 APPLICANT: Bausch & Lomb Pharmaceuticals, Inc.

DRUG PRODUCT: Albuterol Sulfate Inhalation Solution, 0.083%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Comparison of pouches		
Layer	**Bausch & Lomb Pharmaceuticals' Albuterol Sulfate Inhalation Solution Pouch**	**(cromolyn sodium inhalation solution) Pouch**
Liner/Sealant (product contact layer)		
Foil		
Outer coating		

We are also providing information related to the toxicity of
OSHA and ACGIH have proposed a 20 ppm permissible exposure limit (PEL) for based on 8 hours per day exposure on a continuous basis. A copy of the proposed OSHA ruling is provided in Attachment 4. A search of the literature has also revealed a number of articles which support the safety of via the inhalation pathway at concentration equal to or greater than those in the proposed OSHA rule. We believe that the proposed OSHA limits provide sufficient proof of the safety of the concentrations present in our product. We can provide additional studies if you wish to see them. Based upon previously provided information, however, we do not believe they are warranted at this time.

We believe this information demonstrates both the equivalence of the Bausch & Lomb pouch material to materials presently in the market and the safety of via the inhalation pathway at concentrations significantly greater than those present in our product.

We also wish to acknowledge a comment made by the Agency during the December 15, 1999 teleconference regarding FDA's December 10,1999 facsimile. During that conference, Mike Smela indicated that we could switch to a foil which is currently approved by the FDA without making an exhibit batch since the stability of our product has already been demonstrated.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's December 10, 1999 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7700 extension 7102.

Sincerely,

Joseph B. Hawkins
Manager, Regulatory Affairs

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-358
APPLICANT: Bausch and Lomb Pharmaceuticals
DRUG PRODUCT: Albuterol Sulfate Inhalation Solution, 0.083%

The Deficiency presented below represents a MINOR Deficiency.

Based on the information provided in your amendment dated 11/04/99, we believe that the contamination of in your drug product is of concern. We believe that you have two options:

- Provide a safety information package for based on the inhalation administration at the concentration level found in your product. We will send it to the Division of Pulmonary Drug Products for consultation.

- Or you may obtain a new overwrap/pouch system, supported by adequate analytical data to demonstrate that it will not contaminate the drug product solution with any volatile chemicals. Chromatographic profiles are requested comparing freshly manufactured solution versus solution stored in the exact market configuration for at least 3 months at 40°C. The sensitivity of the methods should be demonstrated to be approximately 100 ppb using marker compounds. Alternatively, you may provide documentation that the pouch you propose to use has been approved by the FDA for marketing an inhalation solution in We will consider alternate scientific approaches to address this issue.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Pharmaceuticals, Inc. 8500 Hidden River Parkway 813 975 7700
Tampa FL 33637 Fax 813 975 7770

BAUSCH
& LOMB

November 24, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Gratuitous Amendment

Dear Sir or Madam:

The purpose of this correspondence is to amend our November 24, 1999 response to the Agency's September 15, 1999 "not approvable" letter for the above referenced application and to correct an error noted on the 356h submitted with that response.

Question A.1 of the September 15, 1999 letter requested additional information on the presence of . in our product. Our response provided a validated method and data which indicated that id was present in our product and absent from the Reference Listed Drug product. Since that time we have obtained data which demonstrates that is present in a currently marketed inhalation product. We have developed a validated method for in cromolyn sodium inhalation solution and performed testing on Solution (cromolyn sodium inhalation solution). The results of our testing demonstrate that id is present in solution in amounts exceeding 1 ppm. A copy of method is attached.

It has also come to our attention that the 356h provided with our November 24, 1999 correspondence referenced the wrong application. The correct 356h is included with this correspondence.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

NOV 26 1999

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7700 extension 7102.

Sincerely,

Joseph B. Hawkins
Manager, Regulatory Affairs

Enclosure

Pharmaceuticals, Inc. 8500 Hidden River Parkway Tampa FL 33637 813 975 7000 Fax 813 975 7770

November 4, 1999

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Minor Amendment

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's September 15, 1999 "not approvable" letter for the above referenced application. In that letter the Agency indicated that our response would be considered a minor amendment.

To facilitate the Agency's review, each of the questions and our corresponding response is provided in the text of this letter. Necessary supporting documentation for each response is provided in attachments to this amendment.

A.1. In the amendment dated August 12, 1999, you made the following statement:

> **"Furthermore, a scan of containing polymer (at a level of 2 ppb of d) showed absorption at low wavelength (~220 nm) whereas the water extract sample (wherein purified water was placed in intimate contact with the pouch material inside a sealed pouch and stored at 60°C for 4 days) showed a flat baseline, suggesting that no migration was observable even under these stress conditions."**

Please provide your validated analytical method and detailed data (spectra) to support your justification regarding the possibility of contamination to the drug product. The method must be able to detect in the ppb range.

Response: A copy of our validated analytical method is provided in Attachment 1a. The method has been validated with an LOD of 25 ppb and an LOQ of 50 ppb for β-i in the range of 50 to 300 ppb. The method has also been validated with an LOD of 50 ppb and an LOQ of 100 ppb for α-d in the range of 100 to 10,000 ppb. A summary of test data for samples of product is provided in Attachment 1b. As indicated in the summary,

Rev. 11-9-99

the maximum concentration of α- observed for product stored under the labeled conditions (2 - 8°C) is 647 ppb. The concentration of appears to increase with time and temperature and also with decreasing package size (smaller volume of product relative to package material surface area). The samples represent all submitted packaging configurations and the following conditions:

- Newly made product which has never been pouched.
- Product stored in the pouch for 3 months at 2 - 8°C, then removed from the pouch and stored (one sample at 2 - 8°C and another at 25 ± 2°C) for one month prior to testing.
- Product stored in the pouch for 4 month at the labeled (2 - 8°C) storage conditions.
- Product stored in the pouch for 23 months at the labeled (2 - 8°C) storage conditions.
- Product stored in the pouch for 1 month at accelerated (25 ± 2°C) storage conditions.
- Product stored in the pouch for 23 months at accelerated (25 ± 2°C) storage conditions.

Spectra for product stored at each of the above listed conditions are provided in Attachment 1c.

A.2. Please tighten your proposed specification for the "Minimum Fill Volume" of your finished product. The fill volume should not be allowed below the label amount (3.0 mL). An excess volume is recommended to permit sufficient withdrawal and administration of the label volume. Your specification should be

Response: The specification for finished product "Minimum Fill Volume" has been revised to as requested. A copy of the revised finished product release specification is provided in Attachment 2.

A.3. In addition, please also state your specifications (target and range) for the "Minimum fill Volume" used for your in-process controls.

Response: The in-process "Minimum Fill Volume" control has a target value of and specifications of mL and . A copy of the revised In-Process Fill Weight/Volume Measurement form, which list the target and specification values, is provided in Attachment 3.

B. In addition, Bausch & Lomb Pharmaceuticals acknowledges the following:

1. The Agency's request for additional stability data, if available.

2. That Microbiological review for your validation data for process is pending. Microbiological comments were received with the Agency's September 15, 1999 facsimile, and have been addressed under separate cover. A copy of the cover letter for that response is provided in Attachment B.2.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's September 15, 1999 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7700 extension 7102.

Sincerely,

JB. Hawk

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

Pharmaceuticals, Inc. 8500 Hidden River Parkway 813 975 7700
Tampa FL 33637 Fax 813 975 7770

October 1, 1999

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
AS

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Response to Microbiology Deficiencies

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's September 15, 1999 "not approvable" facsimile for the above referenced application. In that correspondence the Agency indicated that our response would be considered a minor amendment.

To facilitate the Agency's review, each of the microbiology questions and our corresponding response is provided in the text of this letter. Chemistry responses will be provided under separate cover. Necessary supporting documentation for each response is provided in attachments to this amendment.

Page(s) 4

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

10/1/99

resin is typically closer to providing further reduction in the possible frequency of contamination. The summaries provided in the original application also confirm that the manufacturing process produces containers suitable for sterile product.

We believe that this correspondence provides a thorough response to the microbiology questions raised in the Agency's September 15, 1999 facsimile. As such, we hope that a rapid review and subsequent product approval will be forthcoming.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7700 extension 7102.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-358
APPLICANT: Bausch and Lomb Pharmaceuticals
DRUG PRODUCT: Albuterol Sulfate Inhalation Solution, 0.083%

The Deficiencies presented below represent MINOR Deficiencies.

A. Deficiency:

1. In the amendment dated August 12, 1999, you made the following statement:

   "Furthermore, a containing polymer (at a level of 2 ppb of showed absorption at low wavelength (~210 nm) whereas the water extract sample (wherein purified water was placed in intimate contact with the pouch material inside a sealed pouch and stored at 60°C for 4 days) showed a flat baseline, suggesting that no migration was observable even under these stress conditions."

   Please provide your validated analytical method and detailed data to support your justification regarding the possibility of contamination to the drug product. The method must be able to detect in the ppb range.

2. Please tighten your proposed specification for the " " of your finished product. The fill volume should not be allowed below the label amount (3.0 mL). An excess volume is recommended to permit sufficient withdrawal and administration of the label volume. Your specification should be

3. In addition, please also state your specifications (target and range) for the " " used for your in-process controls.

B. In addition to responding to the deficiency presented above, please note and acknowledge the following comment in your response:

1. Please provide additional stability data, if available.

2. Microbiological review for your validation data for aseptic filling process is pending.

Sincerely yours,

cc Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Microbiology Comments to Be Provided to the Applicant

ANDA: 75-358 APPLICANT: Bausch & Lomb Pharmaceuticals

DRUG PRODUCT: Albuterol Sulfate Inhalation Solution, 0.083% (Sterile)

A. Microbiology Deficiencies:

1. The applicant should test the gloves of all personnel involved in the filling process for the drug product.

2. Regarding validation of the ycles:

   a. It was stated that the population and D-value of the biological indicator would be "confirmed by the vendor" (pp. 306, 341). This is unacceptable; at a minimum, the population of the biological indicator should be confirmed by the applicant as part of any validation.

   b. The applicant should report the revalidation frequency of the cycles.

   c. For each system, lidation runs were not considered successful; this seems like an excessive failure rate. The applicant should indicate how they are going to assure the reliability of the ystem.

3. Regarding the drug product solution microbial retention validation data:

   a. The application is not complete without the microbial retention validation data. Please submit the microbial retention validation data for the bulk drug product solution

   b. It was stated that the acceptance criterion for the microbial retention recirculation challenge test would be retention of all the challenge organism by the test membrane. Please clarify how "retention of all of the challenge organisms" will be determined. Will the applicant confirm the sterility of the

4. Regarding the e applicant should submit information and data concerning the validation of the sterilization of the e system.

Pharmaceuticals, Inc. [illegible] Fax 813 975 7770

August 12, 1999

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Facsimile Amendment

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's July 14, facsimile for the above referenced application. In that letter the Agency indicated that our response would be considered a Facsimile amendment.

To facilitate the Agency's review, each of the questions and our corresponding response is provided in the text of this letter. Necessary supporting documentation for each response is provided in attachments to this amendment.

A1. **CDER has recently received data that certain overwraps/pouches used to protect inhalation solutions may contaminate the product with volatile chemicals. Please provide analytical data that the pouch you will use will not contaminate the solution with volatile chemicals. Chromatographic profiles are requested comparing freshly manufactured solution versus solution stored in the exact market configuration for at least 3 months under accelerated conditions. The sensitivity of the methods should be demonstrated to be approximately 100 ppb using marker compounds. Alternatively, you may provide documentation that the pouch you propose to use has been approved by the FDA for marketing an inhalation solution in We may consider alternate scientific approaches to address this issue.**

Response: The material used for our overwraps/pouches, described on page 938 of the original ANDA submission (provided in Attachment 1), is primarily an aluminum foil which contains laminates of polymeric materials. The only laminate layer inside the foil) acts a moisture barrier and as a lining on the foil. is comprised chemically of a poly(ethylene/methacrylic acid). This polymeric material may contain traces of unreacted d typically in the order of less than 200 ppm. The safety of such res

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

material has been established based on animal feeding experiments (at levels as high as 10% of resin) of the resin as well as using low molecular weight fraction extracted from the resins. The results of long term studies indicated no pathologic changes observed. Thus, the safety of such materials is assured (which is consistent with the Agency's view as expressed in the July 1999 Guidance for Container-Closure systems).

Based on the review of scientific literature (References 1-5) pertaining to the migration of components from polymeric films and/or packaging films into polyethylene containers, it can be surmised that the possibility of migration of low to medium molecular weight aromatic compounds is unlikely. In one study it was demonstrated that migration of a variety of lipophilic and organic stabilizers from polymer containing packaging material was dictated by diffusion of migrant within the polymer, which was typically very low for aqueous containing packages. This is consistent with the widely held theory that apolar and hydrophobic compounds would not migrate into aqueous based products.

In the specific case of the basic polymer is a high molecular weight water insoluble substance. Low molecular weight oligomers may be expected to migrate into suitable highly non-polar solvents, such as hexane. This is reasonable to expect based on some preliminary observations conducted in developmental studies. Gas chromatographic analysis of water extracts (wherein purified water was placed in intimate contact with the pouch material inside a sealed pouch and stored at 60 °C for 4 days) indicated absence of semi-volatile to volatile constituents. This gas chromatographic method is capable of detecting a range of 20 or more solvents, including but not limited to benzene, toulene, cyclopentanone, cyclohexene, acetonitrile, dichloromethane, methylethylketone. The limit of detection of a typical solvent such as toulene using this method is estimated to be 2 ppm. Furthermore, a containing polymer (at a level of 2ppb of showed absorption at low wavelengths (~ 210 nm) whereas the water extract sample showed a flat baseline, suggesting that no migration was observable even under these stress conditions.

It is noteworthy that the stability data to date indicate no significant difference in chromatographic profile with respect to time zero, especially when using a sensitive assay method for the primary analyte. This method has a limit of detection of approximately 160 ppb (for the primary analyte).

Based on these observations and assertions from the vendor of the material of construction of these pouches, assurance from the vendor that the

construction material used for the cartons contains no vanillin, coupled with available scientific literature it is reasonable to state that the extent of migration, if any, from the pouches should not be a safety or product quality concern.

Bausch & Lomb Pharmaceuticals also acknowledges:

B1. The Agency's request for additional stability data. Current stability data for the exhibit lot was provided in the previous (June 9, 1999) submission. No additional results are available at this time

B2. That the microbiological review of validation data submitted is pending.

B3. That labeling changes requested by the Agency must also be addressed. The requested changes have been implemented in our current labeling, provided in Attachment 2.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's May 26, 1999 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7700 extension 7102.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

References:
Ref. 1. Packaging Technology Sciences, (1996), 9(3), 143-152
Ref. 2. Fresenius' Journal of Analytical Chemistry, (1996), 354(4), 483-489
Ref. 3. S.T.P.Pharma, (1986), 2(14), 231-234
Ref. 4. Int. Symp. Migr., 4th (1983), 83-104
Ref. 5. Plast. Rubber Process. Appl., (1984), 4(1), 53-62

Pharmaceuticals, Inc.
Tampa FL 33637
FAX 813 975 7777

June 9, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

ANDA 75-358 AMENDMENT
N/A-1

Re: ANDA 75-358
Albuterol Sulfate Inhalation Solution, 0.083%
Minor Amendment

Dear Sir or Madam:

The purpose of this correspondence is to respond to the Agency's May 26, 1999 "not approvable" letter for the above referenced application. In that letter the Agency indicated that our response would be considered a minor amendment.

To facilitate the Agency's review, each of the questions and our corresponding response is provided in the text of this letter. Necessary supporting documentation for each response is provided in attachments to this amendment.

A1. Referenced DMF is inadequate per FDA's recent letter to the DMF holder. Please confirm a response from the DMF holder before you submitresponse to this letter.

Response: as responded to FDA's recent letter. A letter from to that effect is provided in Attachment 1.

Bausch & Lomb Pharmaceuticals also acknowledges:

B1. The Agency's request for additional stability data. Current stability data for the exhibit lot is provided in Attachment 2.

B2. That the microbiological review of validation data submitted is pending.

B3. That labeling changes requested by the Agency must also be addressed. The requested changes have been implemented in our current labeling, provided in Attachment 4.

B4. That validation of the regulatory methods has not been completed. Bausch & Lomb Pharmaceuticals commits to work with the Agency to resolve any issues which may arise during their evaluation of methods.

CENTER FOR DRUG EVALUATION
JUN 10 1999
RECEIVED

In addition, we wish to amend our application beyond the scope of the Agency's May 26, 1999 "not approvable" letter. Specifically, we wish to correct an error in the original submission. The wrong Albuterol Sulfate certificate of analysis was provided with the drug substance shipped to us by the vendor. Since the vendor lot number on the certificate of analysis (28-0508) was very similar to the correct lot number (25-0508), the error was not noted at the time and the incorrect lot number was entered on our in-house testing documents. The correct vendor certificate of analysis has been obtained and our in-testing documents have been corrected to reflect the vendor lot number for the material used to manufacture the exhibit batch. Copies of the vendor certificate of analysis for lot #25-0508 and the corrected in-house testing documents are provided in Attachment 3.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

The information contained in this supplement is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

We believe that this correspondence provides a thorough response to the questions raised in the Agency's May 26, 1999 letter. As such, we hope that a rapid review and subsequent product approval will be forthcoming. If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7700 extension 7102.

Sincerely,

Joseph B. Hawkins
Manager,
Regulatory Affairs

Enclosure

ANDA 75-358

Bausch & Lomb Pharmaceuticals Inc.
Attention: Joseph B. Hawkins
8500 Hidden River Parkway
Tampa, FL 33637

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated April 28, 1998 and your correspondence dated April 28, 1998.

NAME OF DRUG: Albuterol Sulfate Inhalation Solution, 0.083% (Sterile)

DATE OF APPLICATION: April 14, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 15, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

April 28, 1998

NEW CORRESPONDENCE

BAUSCH & LOMB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 75-358
Albuterol Sulfate Solution for Inhalation, 0.083%
Telephone Amendment

Dear Sir or Madam:

This amendment is submitted in response to a request, with regard to the above referenced application, made by the Agency's Ms. Denise Huie. The Agency requested clarification of our April 15, 1998 application. Specifically, we were asked to identify the total number of dosage units pouched in each configuration.

The following table identifies the number of units which were packaged in each configuration:

Configuration	4 Units per Pouch	28 Units per Pouch	60 Units per Pouch
Number of Pouches			
Number of Units			

These totals were calculated from the information on page 843 of the application.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of the information contained in this amendment has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph B. Hawkins

Joseph B. Hawkins
Manager,
Regulatory Affairs

RECEIVED
APR 29 1998
GENERIC DRUGS

April 14, 1998

BAUSCH & LOMB
Healthcare and Optics Worldwide

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: Albuterol Sulfate Inhalation Solution, 0.083%
ANDA Submission

Dear Sir or Madam:

In accordance with the provisions set forth in 21 CFR 314.94, we are submitting this abbreviated new drug application, in duplicate, for Albuterol Sulfate Inhalation Solution, 0.083% (Sterile).

An analytical methods validation package, which includes three (3) additional copies of non-compendial assay procedures and their corresponding validation studies, is provided under separate cover.

Standard operating procedures (SOP's) are provided in this application as an aid to the review process. Revisions may be made to these SOP's after appropriate in-house review and approval. Changes which influence the manufacture of Albuterol Sulfate Inhalation Solution, 0.083% (Sterile), will be reported to the Agency as established in 21 CFR 314.70.

In accordance with 21 CFR 314.94 (d)(5), we certify that a true copy of the information contained in this application has been forwarded to FDA's Orlando District Office.

If you have any questions regarding this correspondence, please contact me at the above address or by telephone at (813) 975-7775.

Sincerely,

Joseph B. Hawkins

Joseph B. Hawkins
Manager,
Regulatory Affairs

enclosure